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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,723	01/17/2001	Yasuo Koishihara	53466/295	4861

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EXAMINER	
EWOLDT, GERALD R	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 03/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

HC

Office Action Summary	Application No.	Applicant(s)	
	09/760,723	KOISHIHARA, YASUO	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2004 and 13 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-24* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13 and 15-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed 1/13/05 in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's amendment and remarks, filed 9/14/04, have been entered.

2. In view of Applicant's amendment, in particular the newly added limitation that lymphocytes be inhibited without killing them, the previous rejections of Claims 13-22 have been withdrawn.

3. Claim 14 stands withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species.

Claims 13 and 15-24 are being acted upon.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 23 and 24 stand rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,298,420 (1994) in view of Goto, T., et al. (1994, IDS) for the reasons of record set forth in the paper mailed 9/22/03.

Applicant's arguments, filed 9/14/04, have been fully considered but they are not persuasive. Applicant has provided no additional arguments and states only, "As Applicant previously explained, Chang and Goto do not teach or suggest a method of inhibiting B lymphocyte activation; rather, Chang merely describes a method of killing B lymphocytes via antibody-dependent cellular cytotoxicity (ADCC). Also, Chang and Goto provide no evidence that HM1.24 actually plays a functional role in multiple myeloma, and therefore do not teach or suggest the use of HM1.24 antibodies to treat that condition".

As set forth previously, killing the lymphocyte would inhibit its activation (thus, meeting the limitations of the claims) and a functional role for HM1.24 in multiple myeloma is irrelevant; the reference clearly establishes that HM1.24 is a mature B cell marker rendering it a suitable target for antibody therapy.

6. The following are new grounds for rejection.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 13 and 15-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically:

A) the specification provides insufficient evidence that the anti-HM1.24 antibody actually binds the amino acid sequence of SEQ ID NO:1,

B) the specification provides insufficient evidence that the antibody employed in the claims could bind T lymphocytes as is required by the claimed method,

C) the specification provides insufficient evidence that the claimed method could inhibit lymphocyte activation without killing the lymphocytes.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The

"amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Given the inherent unpredictability of physiological activity, which would include biological processes, a certain amount of enablement beyond mere assertion must be required.

Regarding A), it is noted that the only antibody disclosed in the specification is the anti-HM1.24 antibody of Goto et al. (1994, of record). The specification implies, and the claims recite, that the anti-HM1.24 antibody binds the amino acid sequence of SEQ ID NO:1, yet neither the specification nor Goto et al. establish said binding. Indeed, Goto et al. provides no sequence for the antibody's ligand at all; the reference merely states that the antibody is B cell specific and the specification provides no nexus (i.e., insufficient direction) between SEQ ID NO:1 and the anti-HM1.24 antibody. Accordingly, the use of the anti-HM1.24 antibody for binding the amino acid sequence of SEQ ID NO:1 must be considered to be highly unpredictable and requiring of undue experimentation.

Regarding B), a further review of Goto et al. shows that the reference teaches that the anti-HM1.24 antibody is B cell specific. Table 1 teaches that the antibody does not bind T cells. Thus, the teachings of Goto et al. directly contradict the findings of the instant disclosure. The most scientifically reasonable conclusion would be that the antibody binds some T cells (i.e., the T cells of the specification), but not others (i.e., the T cells of Goto et al.). Clearly then, an unpredictability has been established, at least as the claimed invention encompasses a method that requires the binding of the amino acid sequence of SEQ ID NO:1 and the binding of T cells.

Regarding C), a review of the specification discloses two Examples relevant to the method of the instant claims. In Example 2, the effects of anti-HM1.24 antibody on antibody production of human B cells is measured. In Example 3, the effects of anti-HM1.24 on the uptake of ^{3}H-thymidine by activated

T cells was measured. The results of Example 2 were, "the addition of 20 ug/ml antibody completely inhibited IgG production. It was indicated, therefore, that anti- HM1.24 antibody inhibited the activation of B cells" (page 30). The results of Example 3 were, "The result as shown in Fig. 2 revealed that T cell activation by PHA is accompanied by the expression of HM1.24 antigen on the cells", (page 31) and "The result as shown in Fig. 4 revealed that blast formation by PHA-stimulated T cells caused an increase in the incorporation of ^{3}H-thymidine, and that the addition thereto of control mouse IgG2a at 20 ug/ml caused no changes while that of anti-HM1.24 antibody at 20 ug/ml inhibited the incorporation of 3H-thymidine. It was hence indicated that anti-HM1.24 antibody inhibits the activation of T cells" (page 32). Note that in neither Example was the viability of the anti-HM1.24 antibody treated cells measured. Thus, it is merely asserted that the antibody inhibits activation without killing the lymphocytes. This assertion, however, is contradicted by the prior art. See, for example EP0960936. In Example 13 at page 37, the reference teaches that when human peripheral blood cells are bound by a humanized anti-HM1.24 antibody, ADCC (antibody-dependent cell-mediated cytotoxicity) occurs, i.e., the cells are killed. Example 14 further teaches that the antibody has an anti-B cell tumor effect *in vivo*. It is highly unlikely that the anti-tumor effect is due to cellular inhibition; the most reasonable explanation for the anti-tumor effect is ADCC. See, for example, Stites et al. (1987) wherein it is taught that anti-tumor ADCC functions through the killing of tumor cells. Accordingly, the method of the instant claims must again be viewed as highly unpredictable, and in light of the prior art, requiring of undue experimentation.

9. Claims 13 and 15-22 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

A method of inhibiting lymphocyte activation <u>without killing lymphocytes</u> (Claim 13).

Applicant indicates that support for the new limitation can be found at pages 23-25 and Example 2 of the specification.

A review of the specification fails to reveal support for this new limitation. In particular, page 22 discloses only that the cells are not activated, there is no teaching that the cells are alive. Likewise, page 24 teaches only the assay for a lack of (or change in) expression of activation markers; said lack could very well be due to the fact that the cells were killed (also note that the disclosures at pages 23-25 relate only to the use of the anti-HM1.24 antibody and could not support the generic claims). Similarly, there is no disclosure in Example 2 that the cells are not killed by the anti-HM1.24 antibody.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 13 and 15-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, specifically:

"an antibody that binds to a protein having an amino acid sequence as set forth in SEQ ID NO:1," is vague and indefinite as SEQ ID NO:1 comprises a DNA sequence.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571)272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

14. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

2/23/05

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Primary Examiner
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